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10/566,535	04/27/2006	Kiyotaka Shiba	4439-4039	3547

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	**PAPER NUMBER**
1654	

NOTIFICATION DATE	DELIVERY MODE
05/16/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/566,535	SHIBA ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2008* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/10/08, 7/2/07, 6/7/06, 1/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. The restriction requirement mailed 2/12/2008 is vacated. SEQ ID NOs: 1-38 are free of the art.

Priority

2. Receipt is acknowledged of papers submitted to the International Bureau in PCT/JP04/11319 under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Sequence Compliance

3. This application is objected to because the amino acid and nucleic acid sequences in the abstract and in figures 3, 4, 8, 10 and 18 are not associated with a sequence identifier (a SEQ ID NO). All sequences longer than ten nucleotides or four amino acids referenced in the specification must include a SEQ ID NO and must be included in the Sequence Listing. See MPEP § 2421-2422. Correction is required.

Specification

4. The use of the trademark Expand Long Template PCR System has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

5. Claims 5, 10, 34 and 52 are objected to because of the following informalities: phrases referring to positions in the amino acid sequence such as "1, 4 and 5th" should be "1st, 4th and 5th" or "first, fourth and fifth.". Appropriate correction is required.

Claim Rejections - 35 USC § 112/101

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27-30, 46-49 and 65-69 provide a method for the use of titanium, silver and silicone binding peptides, respectively, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 27-30, 46-49 and 65-69 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 4, 5, 8, 9, 13, 15-31, 33, 34, 37-49, 51, 52, and 55-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include: 1) the scope of the invention; 2) actual reduction to practice; 3) disclosure of drawings or structural chemical formulas; 4) relevant identifying characteristics including complete structure, partial structure, physical and/or chemical properties, and structure/function correlation; 5) method of making the claimed compounds; 6) level of skill and knowledge in the art; and 7) predictability in the art.

Scope of the Invention

The claims are drawn to titanium, silver and silicone-binding peptides comprising SEQ ID NOs: 1-38 wherein at least one amino acid is deleted, substituted or added.

Actual Reduction to Practice

The titanium, silver and silicone-binding peptides comprising SEQ ID NOs: 1-38 were reduced to practice at the time of filing. Titanium, silver and silicone-binding peptides comprising SEQ ID NOs: 1-38 wherein at least one amino acid is deleted, substituted or added were not reduced to practice.

Disclosure of Drawings or Structural Chemical Formulas

The specification does not include drawings or structural chemical formulas representing titanium, silver and silicone-binding peptides comprising SEQ ID NOs: 1-38 wherein at least one amino acid is deleted, substituted or added suitable for use in the claimed invention.

Relevant Identifying Characteristics

Complete structure: The specification presents titanium, silver and silicone-binding peptides comprising SEQ ID NOs: 1-38. The specification does not present the complete structure of titanium, silver and silicone-binding peptides comprising SEQ ID NOs: 1-38 wherein at least one amino acid is deleted, substituted or added.

Partial Structure: The specification does not present the partial structure of titanium, silver and silicone-binding peptides comprising SEQ ID NOs: 1-38 wherein at least one amino acid is deleted, substituted or added..

Physical and/or chemical properties: The specification states that the claimed inventions should be capable of binding to titanium, silver and/or silicone. The specification fails to describe the chemical and physical properties of peptides that are responsible for titanium, silver and silicone-binding.

Structure/Function Correlation: The specification fails to correlate the amino acid sequence of the claimed peptides with the function of titanium, silver and silicone binding.

Method of Making the Claimed Compounds

Methods of synthesizing peptides using recombinant techniques and solid phase chemical synthesis methods are well known in the art.

Level of Skill and Knowledge in the Art

It is within the skill of those in the art to make additions, deletions and substitutions in peptides and to test the resulting peptides for titanium, silver and silicone binding. It is not within the skill of the art to predict which amino acids should be added, deleted and substituted and at which positions in order to improve or at least preserve the titanium, silver and silicone-binding properties of the parent sequence.

Predictability in the Art

The level of unpredictability in the peptide design art is high. Even when a protein structure is known and its activity well-established, it is difficult to predict the effect of individual amino acid substitutions or deletions. Rudinger (Peptide Hormones (Ed. J.A. Parson). University Park Press. Baltimore, 1976, pp. 1-7) states: "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." Recent examples in the art suggest that Rudinger's assessment of the unpredictability of amino acid substitution effects is still valid. Pitt *et al.* (*Nuc. Ac. Res.*, **2000**, *28*, 4419) report that random mutagenesis of the σ^{54} RNA polymerase uncovered five independent single amino acid substitutions that lead to defective transcription. Bradley *et al.* (*J. Mol. Biol.*, **2002**, *324,* 373) demonstrate that an Ala -> Gly substitution in six analogous structural environments of an ankyrin repeat protein have remarkably diverse effects on protein stability. Flanagan *et al.* (*Proc. Natl. Acad. Sci. USA*, **1992**, *89*, 748) show that the deletion of thirteen amino acids from the C-terminus of the 149-residue staphylococcal nuclease results in a loss of 50% of the helicity but does not cause the protein to unfold into a disordered chain. A dramatic example of the effect of single amino acid substitutions is in sickle cell anemia. This disease, characterized by chronic haemolysis and

susceptibility to infection, is caused by a single Glu -> Val substitution in the β-globin gene (Schnog *et al. J. Med.*, **2004**, *62*, 364). Finally, Sawai *et al.* (*Prot. Engin.*, **2002**, *15*, 225) show that this lack of predictability extends to short peptides as well: specific single amino acid substitutions in an eighteen-residue antimicrobial peptide dramatically reduce toxicity and affect the structure of the peptide in subtle ways.

When the above factors are weighed, one of ordinary skill in the art would not recognize that Applicant was in possession of the full scope of claimed titanium, silver and silicone-binding peptides at the time of filing. Only peptides comprising SEQ ID NOs: 1-38 meet the written description requirement of 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, second paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 6, 10, 12, 13 and 27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 6 recites the limitation "the 2nd lysine" in SEQ ID NO: 2. There is insufficient antecedent basis for this limitation in the claim because SEQ ID NO: 2 does not include two lysine residues. Furthermore, SEQ ID NO: 1, which is referred to in the parent claim, like wise does not include two lysine residues.

12. Claim 10 recites the limitation "The titanium-binding peptide according to claim 8, comprising amino acid sequences shown in SEQ ID NOs: 4 to 14, wherein the 1 to 5th and 7 to 12th amino acid residues are substituted by alanine, respectively." Claim 8 recites SEQ ID NO: 3

in which one or more amino acids is substituted. It is not clear whether claim 10 is drawn to eleven peptides in which positions 1-5 and 7-12 of SEQ ID NO: 3 are individually substituted by alanine, or whether claim 10 is drawn to peptides comprising SEQ ID NOs: 4-14 in which position 1-5 and 7-12 are substituted with alanine, respectively. The construction of claim 10 is indefinite because it is not clear which peptide is the parent peptide being substituted with alanine.

13. Claims 12 and 13 recite the limitation "The titanium binding peptide comprising amino acid sequences shown in SEQ ID NOs: 16 to 24." Two alternative interpretations exist for this limitation. First, the claim may be a drawn to a single titanium binding peptide comprising each of SEQ ID NOs: 16 to 24. Second, the claim may be drawn to a titanium binding peptide selected from the group consisting of SEQ ID NOs: 16 to 24. These alternative interpretations render claims 12 and 13 indefinite.

14. Claims 14 and 15 recite the limitation "A titanium binding peptide comprising an amino acid sequences shown in SEQ ID NOs: 25 to 38." Two alternative interpretations exist for this limitation. First, the claim may be a drawn to a single titanium binding peptide comprising each of SEQ ID NOs: 25 to 38. Second, the claim may be drawn to a titanium binding peptide selected from the group consisting of SEQ ID NOs: 25 to 38. These alternative interpretations render claims 14 and 15 indefinite.

15. Claims 3-69 recite the limitation “shown in SEQ ID NO:". Two alternative interpretations exist for this limitation. First, the peptides comprise amino acid sequence SEQ ID NO: x in its entirety. Second, the peptides comprise a fragment of SEQ ID NO: x that is shown in the sequence.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 2, 16-24, 27-29 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Zreiqat *et al.* (*J. Biochem. Mat. Res.*, **2003**, *64A*, 105-13, available online 22 Nov. 2002, cited on Information Disclosure Statement filed 1/10/2008). Zreiqat *et al.* teach a titanium binding peptide comprising a titanium binding sequence, GGGGGC, and a functional sequence known to affect osteoblast adhesion, GRGDSP (Table 1). With respect to claim 16, the peptide is chemically modified with titanium (page 106, second column). With respect to claim 17, the titanium is a titanium alloy Ti_6Al_4V (page 106, second column). With respect to claims 19-21, the peptide is a conjugate of a titanium binding peptide and a functional peptide having a cell adhesion ability (page 106, first column). With respect to claim 22, the peptide forms a complex with titanium (page 106, second column). With respect to claim 23, the peptide comprises a titanium binding region and a peptide tag, GRGDSP (page 106, first column). With respect to claim 24, the peptide forms a complex with titanium (page 106, second column). With respect to claims 27-29 and 31, Zreiqat *et al.* teach a method of refining a titanium surface using the titanium-binding peptide GRGDSPGGGGGC (page 110, first column) and an implant material

comprising titanium and the titanium-binding peptide GRGDSPGGGGGC (page 112, first column).

With respect to claim 2, Zreiqat *et al.* do not teach that the peptide was obtained from a phage display screening method. Section 2113 of the MPEP states: "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In the instant case, the peptide taught by Zreiqat *et al.* meets the functional limitation of the claim that the peptide be capable of binding to titanium. Therefore, Zreiqat *et al.* anticipate the claims.

18. Claims 1, 2, 16-18, and 23-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Beyer *et al.* (U.S. Publication No. 2006/0051395). Beyer *et al.* teach a method of screening phage display libraries for peptides that bind to titanium beads (example 1) comprising the steps of contacting titanium beads with a population of phage expressing a library of different peptide sequences, recovering titanium bound to phage particles, proliferating the obtained phage particles in *E.coli*, repeating the panning operation with the proliferated titanium binding phage and concentrating proliferating titanium binding clones. Beyer *et al.* also teach titanium binding peptides obtained by the phage display screening method (paragraph 0064). With respect to claims 16 and 23, Beyer *et al.* teach that the titanium binding peptides were chemically modified with biotin (paragraph 0065). With respect to claim 17, the titanium is a titanium alloy Ti_6Al_4V (paragraph 0060). With respect to claim 18, a titanium-peptide complex is formed as part of the

phage display screening method (paragraph 0061). With respect to claim 24, Beyer *et al.* teach the conjugation of the peptides to biotin and the binding of the resulting conjugates to titanium (paragraph 0065). With respect to claim 25, Beyer *et al.* teach a titanium binding phage expressing a titanium binding peptide on the particle surface (paragraph 0061). With respect to claim 26, Beyer *et al.* teach a phage particle expressing a titanium-binding peptide, bound to titanium (paragraph 0061).

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1, 2, 16-29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naik *et al.* (U.S. Publication No. 2006/0035223) in view of Zreiqat *et al.* (*J. Biochem. Mat. Res.*, **2003**, *64A*, 105-13, available online 22 Nov. 2002, cited on Information Disclosure Statement filed 1/10/2008). Naik *et al.* teach a method of identifying and isolating peptides which can bind silica or other inorganic materials comprising screening a phage display peptide library (abstract). Naik *et al.* do not teach that the phage display method can be used to isolate peptides that bind to titanium. Zreiqat *et al.* teach titanium-binding peptides.

It would have been obvious to one of ordinary skill in the art to use the phage display screening method taught by Naik *et al.* to screen for peptides that bind to titanium. The skilled artisan would have been motivated to isolate titanium-binding peptides based on the work of Zreiqat *et al.* that illustrates that such peptides can be useful in methods of enhancing osseointegration which is crucial for prosthetic fixation (abstract). The skilled artisan would have been motivated to use phage display based on the teachings of Naik *et al.*: "In the biological arts, it has long been known to utilize a phage display library to express a particular protein. Phage peptide display is a selection technique in which random peptides from a library are expressed as a fusion with a phage coat protein, resulting in the display of the fused protein on the surface of the phage particle. The advantage of phage display technology is that it can offer the ability to identify surface-specific proteins in a more practical way and avoid the lengthy and complex identification procedures associated with traditional protein isolation and gene sequencing." (paragraph 0004). There would have been a reasonable expectation of success given that Naik *et al.* teach the isolation of peptides that bind to silver by this method (paragraph 0087) and that phage display libraries are commercially available (paragraph 0027).

With respect to claim 2, it would have been obvious to isolate a titanium-binding peptide from this method (Naik *et al.*, paragraph 0004). With respect to claims 16 and 23, the peptide is chemically modified with titanium as part of the phage display process (Naik *et al.*, paragraph 0004) With respect to claim 17, the titanium is a titanium alloy Ti_6Al_4V (Zreiqat *et al.*, page 106, second column). With respect to claims 19-21, the peptide is a conjugate of a titanium binding peptide and a functional peptide, the phage coat proteins, which have a cell adhesion ability (Naik *et al.*, paragraph 0004). With respect to claim 22, the peptide forms a complex with

titanium (Naik *et al.*, paragraph 0004). With respect to claim 23, the peptide comprises a titanium binding region and a peptide tag, the phage coat protein (Naik *et al.*, paragraph 0004). With respect to claim 24, the peptide forms a complex with titanium (Naik *et al.*, paragraph 0004). With respect to claim 25, Beyer *et al.* teach a titanium binding phage expressing a titanium binding peptide on the particle surface (paragraph 0061). With respect to claim 26, Beyer *et al.* teach a phage particle expressing a titanium-binding peptide, bound to titanium (paragraph 0061).

With respect to claims 27-29 and 31, it would have been further obvious to conjugate the titanium-binding peptide isolated from a phage display screening method to the GRGDSP peptide taught by Zreiqat *et al.* and to use it a method of refining a titanium surface using the titanium-binding peptide (Zreiqat *et al.*, page 110, first column) and in an implant material (Zreiqat *et al.* page 112, first column). The skilled artisan would have been motivated to do so because as a titanium-biding peptide, it could substitute for the GGGGGC sequence taught by Zreiqat *et al.*

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

21. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday, Tuesday, Thursday-Friday, 9:00 A.M. to 3:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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